REMARKS

Claims 1-18 and 20-46 are now pending in the application. Claims 1, 10, 20, 29, 38, and 43 have been amended, and claims 47-52 have been added. No new matter has been added. Support for added claims 47-48 and 50-51 can be found, for example, at page 11, line 26 to page 12, line 9. Support for added claims 49 and 52 can be found, for example, at page 17, lines 16-31. Reconsideration and reexamination are respectfully requested in view of the amendments and the following remarks.

Claim Rejections 35 USC § 103

The Examiner rejected claims 1-18 and 20-46 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6, 804,410 ("Lennon et al.") in view of U.S. Patent No. 6,683,316 ("Schamber et al.").

With respect to independent claims 1 and 20, the Examiner indicated that Lennon et al. teach all of the elements of "a method of calibrating an ion source" except "the relationship being determined at least in part by aligning one or more fiducials relative to a reference point of the sample control system, the fiducials defining reference points of the sample plate coordinate system," which is taught by Schamber et al. The applicant respectfully disagrees.

1. The cited references fail to show all of the elements of claims 1 and 20

Neither of the references cited by the Examiner, either alone or in combination, describes or suggests "a method for calibrating an ion source" including "determining a relationship between the coordinate system of the sample plate and a coordinate system of the sample control system, the relationship being determined at least in part by aligning one or more fiducials relative to a reference point of the control system" and "using the determined relationship to align [a] target region[] of the sample plate," as previously required by claims 1 and 20, where the determing is done using "pattern recognition techniques" and the one or more target regions are "at one or more predefined locations in the sample plate coordinate system" as now explicitly required by claims 1 and 20.

a. The cited references fail to use target regions at predefined locations

Lennon et al. describe a method for aligning the laser of a mass spectrometry apparatus with the samples on a sample plate using "images as feedback to provide value-added direction to the positioning mechanism" (column 3, lines 59-67). The problem addressed by Lennon et al. is that the actual samples sometimes do not occur in the locations where they are expected to occur, as illustrated in Figure 4. Because of this, methods that target the expected sample locations may be unproductive or inefficient. The visual feedback methods of Lennon et al. allow a user to locate the samples, regardless of where they are supposed to be on a sample plate. The user can then improve mass spectrometry analysis of the sample plate by directing the laser of the mass spectrometer to the locations where the samples are actually observed rather than the locations where the samples were expected to be found.

Schamber et al. similarly describe a system for finding a specimen on a carrier in an SEM by acquiring an optical image that can be used to locate the specimen or portions of a specimen in a physical coordinate system. The problem addressed by Schamber et al. is that the location of the specimen or portions of interest on a specimen are generally unknown, such that the user must navigate around the carrier or the specimen to determine a location of interest (See column 1, lines 32-63).

In contrast, the applicant's claimed invention is used to improve the result of ionization in a mass spectrometer where the target regions are "at one or more predefined locations in the sample plate coordinate system." The problem addressed by the applicant is the accuracy of the positioning of the sample plate in the sample control system – not the problem of finding a sample spot on a sample plate or a speciment on a specimen carrier after it has been mounted in the mass spectrometer or microscope.

As explained in the Specification at page 8, lines 4-8, "[a] sample plate 140 includes a predetemined arrangement of target regions – for example, a number of circular wells or depressions, arranged in the form of a regular grid, in which the analyte and matrix molecules are deposited." The sample plate is mounted in a sample holder in the sample control system, which has its own coordinate system (Specification page 10, lines 4-6; "the coordinate system in which

the ... components of system 100 operate"). The relationship between the coordinate system of the sample plate, with its distribution of target regions, and the coordinate system of the sample control system is determined using the claimed methods. The determined relationship is then used to accurately align the ion optics of the mass spectrometer with a target region at a predefined location in the sample plate coordinate system. With the claimed methods, the target region can be more accurately aligned with the ion optics of the mass spectrometer because the relationship between the coordinate system of the sample plate and the coordinate system of the sample control system has been determined, such that discrepancies between the two coordinate systems (e.g. a linear displacement) can be taken into account when aligning the ion optics based on the location of a target region in the sample plate coordinate system (see Specification, page 10, lines 14-24).

Neither Lennon et al. nor Schamber et al. describe or suggest such a method for calibrating an ion source by determining a relationship between a coordinate system of a sample plate and a coordinate system of a sample control system, and "using the determined relationship to align [a] target region[] of the sample plate," where the target region is "at one or more predefined locations in the sample plate coordinate system." For at least this reason, the applicant respectfully submits that claims 1 and 20 are allowable.

b. The cited references fail to show the use of pattern recognition techniques

In addition, neither Schamber et al. nor Lennon et al. describe or suggest the use of "pattern recognition techniques," as now required by claims 1 and 20, to determine a relationship between the coordinate system of the sample plate and the coordinate system of the sample control system by aligning one or more fiducials relative to a reference point of the sample control system.

The use of pattern recognition techniques, as described in the Specification (for example at page 17, line 16 to page 18, line 5), helps make it possible for the system to be fully automated. In a fully automated system, the user plays no part in the registration, calibration, or analysis processes and the system is capable of operating without user intervention once the user has placed the sample plate in the sample plate holder (Id. at page 7, lines 24-27). Thus, the

calibration of the claimed methods does not require that a user search for and locate the sample in order to accomplish the calibration.

Because neither Schamber et al. nor Lennon et al. describe or suggest the use of pattern recognition techniques, the applicant respectfully submits that claims 1 and 20 are allowable.

2. The Examiner has not established motivation to combine the references

The Examiner also suggests that it would have been obvious to use fiducial marks as described in Schamber et al. in the system of Lennon et all, as required by claims 1 and 20. As noted by the Examiner, Schamber explains that two fiducial marks on a specimen carrier can be used to establish the scale of an optical image that is being used to locate portions of interest of a specimen (column 13, lines 28-13). Schamber also states that "the known position of one of these marks may be used to establish the offset for a linear spatial transformation relating the coordinates of the optical image pixels with the coordinates of state drivers" (column 13, lines 31-36).

The applicant respectfully submits, however, that the Examiner has failed to identify any motivation to combine the use of one or two fiducials as described in Schamber et al. with the method of Lennon et al. See *In re Lee*, 277 F.3d 1338, 1345, 1343 (Fed. Cir. 2002) (noting that the PTO "cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies" and emphasizing that "[t]he factual inquiry whether to combine references must be thorough and searching"); see also *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (noting that a showing of a suggestion, teaching, or motivation to combine prior teachings "must be clear and particular . . . . Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'").

The methods described by Schamber et al. involve the use of a scanning electron microscope, or SEM, rather than a mass spectrometer. The fiducials are used to correct for improper positioning of the imaging device, which must be removed "without loss of predictable positioning" (column 6, lines 31-34) when the microscope is mounted over the specimen (see Schamber et al., column 6, lines 6-31 and Figure 1). As explained by Schamber et al, "the

requirement for the hardware component to provide a predictable spatial orientation to the specimen can be relaxed if the software component is implemented so as to make use of fiducial marks in order to establish the required geometrical relationships" (column 7, lines 24-29). In contrast, in the system of Lennon et al. and the system described by the applicant, the imaging device is the imaging device and ion source are fixed and can be simultaneously focused on the sample plate (e.g. Lennon et al. column 2, lines 6-54; Specification, page 8, lines 8-24 and Figure 1;). There is no need to decouple the imaging device in a mass spectrometer.

Because the Examiner has not provided any clear and particular motivation to combine the use of fiducials as described by Schamber et al. with the system and methods of Lennon et al., the applicant respectfully submits that no prima facie showing of obviousness has been made. The applicant therefore submits that claims 1 and 20 are allowable.

For each and all of the reasons discussed above, allowance of claims 1 and 20 is earnestly solicited.

4. Additional claims

Each of claims 2-18, 39-42, and 21-33 depend from claim 1 or claim 20 and is allowable for at least the reasons that the claim from which it depends is allowable, as discussed above. Accordingly, the applicant respectfully submits that dependent claims 2-18, 39-42, and 21-33 are also allowable and such allowance is respectfully requested.

Independent claims 38 and 43 are similar to claims 1 and 20 and allowable at least for the reasons discussed above with reference to claims 1 and 20. Claims 44-46 depend from claim 43 are are also allowable for at least these reasons. Accordingly, allowance of claims 38 and 43-46 is also respectfully requested.

Lastly, the applicant notes that claims 10 and 29 have been re-written to include all of the limitations of the claims from which they depend, in accordance with the Examiner's indication that they would be allowable if so written. The applicant therefore respectfully requests that allowance of claims 10 and 29 be granted.

Enclosed is a check in the amount of $120 for the one-month extension of time fee.

Please apply any other appropriate charges or credits to deposit account 06-1050.

Respectfully submitted,

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